

What is claimed is:

- 1 1. A method for evaluating the morphogenic activity of a candidate morphogenic protein or  
2 analog thereof, the method comprising the steps of:  
3 (a) creating a local permissive defect site in a mammal,  
4 (b) administering a said candidate morphogenic protein or analog systemically to  
5 said mammal, and  
6 (c) measuring the ability of candidate protein or analog to induce new tissue  
7 formation at said defect site.
- 1 2. The method of claim 1 wherein said candidate morphogenic protein or analog is  
2 administered at a site distal to said defect site.
- 1 3. A method for evaluating an optimal dosage of a candidate morphogenic protein or analog  
2 thereof for administering to a mammal, the method comprising the steps of:  
3 (a) creating a local permissive defect site in a mammal, and  
4 (b) administering a said candidate morphogenic protein or analog systemically to  
5 said mammal, and  
6 (c) measuring the ability of candidate protein or analog to induce new tissue  
7 formation at said defect site.
- 1 4. The method of claim 3 wherein said protein or analog is administered at a site distal to  
2 said locus.
- 1 5. The method of claim 1 or 3 wherein said defect locus occurs in skeletal, lung, cardiac,  
2 liver, neural, pancreas, uterine, or thyroid tissue.
- 1 6. The method of claim 1 or 3 wherein said defect locus occur in renal tissue.
- 1 7. The method of claim 1 or 3 wherein said defect locus occurs in dental or periodontal  
2 tissue.
- 1 8. The method of claim 1 or 3 wherein said mammal is aged.

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- 1 9. The method of claim 1 or 3 wherein said mammal has a reduced capacity to induce callus  
2 formation.
- 1 10. The method of claim 1 or 3 wherein said mammal is afflicted with impaired blood flow to  
2 the skeletal extremities.
- 1 11. The method of claim 1 or 3 wherein said mammal has a reduced capacity to induce an  
2 endogenous morphogenetic signal.
- 1 12. The method of claim 1 or 3 wherein morphogenic protein or analog is administered  
2 parenterally.
- 1 13. The method of claim 12 wherein morphogenic protein or analog is administered  
2 intravenously.
- 1 14. The method of claim 1 or 3 wherein said morphogenic protein is administered orally.
- 1 15. The method of claim 1 wherein said morphogenic protein or analog is administered to said  
2 mammal at a time when mesenchymal progenitor cells are accessible to said defect locus.
- 1 16. The method of claim 1, 3 or 4 wherein said morphogenic protein or analog is administered  
2 at least six hours after the creation of said defect.
- 1 17. The method of claim 1 or 4 wherein said morphogenic protein or analog is administered at  
2 least 24 hours after the creation of said defect.
- 1 18. The method of claim 1 or 4 wherein said morphogenic protein or analog is administered at  
2 least 72 hours after the creation of said defect.
- 1 19. The method of claim 1, 3 or 4 wherein said morphogenic protein or analog is administered  
2 to said mammal after the initiation of fibrosis at said defect locus.
- 1 20. The method of claim 1, 3 or 4 wherein said morphogenic protein or analog is administered  
2 in aqueous solution.
- 1 21. The method of claim 8 wherein said mammal is a steroidal drug user.

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- 1 22. The method of claim 8 wherein said mammal is aged, obese, hypertensive, or afflicted with  
2 osteopenia or diabetes.
- 1 23. The method of claim 1 or 3 wherein said morphogenic protein is selected from the group  
2 consisting of: OP1; OP2, OP3, BMP2; BMP3; BMP4; BMP5; BMP6; BMP9; BMP-10,  
3 BMP-11, BMP-12, BMP-15, BMP-3b, DPP; Vg1; Vgr; 60A protein; GDF-1; GDF-3,  
4 GDF-5, GDF-6, GDF-7, GDF-8, GDF-9, GDF-10, GDF-11; and morphogenically active  
5 amino acid sequence variants thereof.
- 1 24. The method of claim 1 or 3 wherein said morphogenic protein is selected from the group  
2 consisting of: OP1; OP2, BMP2; BMP4; BMP5; BMP6; and morphogenically active  
3 amino acid sequence variants thereof.
- 1 25. The method of claim 1 or 3 wherein said morphogenic protein is a morphogen, said  
2 morphogen comprising an amino acid sequence having at least 70% homology within the  
3 C-terminal 102-106 amino acids, including the conserved seven cysteine domain, of  
4 human OP1.
- 1 26. The method of claim 1 or 3 wherein said morphogenic protein is OP1.
- 1 27. The method of claim 1 or 3 wherein said morphogenic protein is mature OP1 solubilized  
2 in a saline solution.
- 1 28. The method of claim 1 or 3 wherein said morphogenic protein comprises an amino acid  
2 sequence defined by OPX (Seq. ID No. 3); Generic Sequence 6 (Seq. ID No. 4, Generic  
3 Sequence 7 (Seq. ID No. 5); Generic Sequence 8 (Seq. ID No. 6); or Generic Sequence 9  
4 (Seq. ID No. 7).
- 1 29. A method for inducing new tissue formation at a nonskeletal defect locus in a mammal,  
2 the method comprising the step of administering morphogenic protein systemically to said  
3 mammal.
- 1 30. The method of claim 29 wherein said morphogenic protein is administered at a site distal  
2 to said locus.

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1 31. A method for enhancing the quantity or quality of callus formation at an morphogenic  
2 defect locus in a mammal, the method comprising the step of administering morphogenic  
3 protein systemically to said mammal at a site distal to said locus.

1 32. A method for enhancing the rate of tissue repair at a local defect site in a mammal, the  
2 method comprising the step of administering an morphogenic protein systemically to said  
3 mammal at a site distal to said locus.

1 33. The method of claim 29, 31, or 32 wherein said defect locus occur in lung, cardiac, liver,  
2 neural, pancreas, uterine, or thyroid tissue.

1 34. The method of claim 29, 31, or 32 wherein said defect locus occur in renal tissue.

1 35. The method of claim 29, 31, or 32 wherein said defect locus dental or periodontal tissue.

1 36. The method of claim 29, 31, or 32 wherein said mammal is a human.

1 37. The method of claim 36 wherein said human has a reduced capacity to induce callus  
2 formation.

1 38. The method of claim 36 wherein said human is afflicted with impaired blood flow to the  
2 skeletal extremities.

1 39. The method of claim 36 wherein said individual has a reduced capacity to induce an  
2 endogenous morphogenetic signal.

1 40. The method of claim 29, 31 or 32 wherein morphogenic protein is administered  
2 parenterally.

1 41. The method of claim 40 wherein morphogenic protein is administered intravenously.

1 42. The method of claim 29, 31, or 32 wherein said morphogenic protein is administered  
2 orally.

1 43. The method of claim 29 wherein said morphogenic protein is administered to said  
2 individual at a time when mesenchymal progenitor cells are accessible to said defect locus.

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1 44. The method of claim 29, 31, or 32 wherein said morphogenic protein is administered at  
2 least six hours after the creation of said defect.

1 45. The method of claim 29 or 32 wherein said morphogenic protein is administered at least  
2 24 hours after the creation of said defect.

1 46. The method of claim 29 or 32 wherein said morphogenic protein is administered at least  
2 72 hours after the creation of said defect.

1 47. The method of claim 29, 31, or 32 wherein said morphogenic protein is administered to  
2 said mammal after the initiation of fibrosis at said defect locus.

1 48. The method of claim 29, 31, or 32 wherein said morphogenic protein is administered in  
2 aqueous solution.

1 49. The method of claim 36 wherein said human is a steroidal drug user.

1 50. The method of claim 36 wherein said human is aged, obese, or afflicted with osteopenia or  
2 diabetes.

1 51. The method of claim 29, 31, or 32 wherein said morphogenic protein is selected from the  
2 group consisting of: OP1; OP2, BMP2; BMP3; BMP4; BMP5; BMP6; BMP9;  
3 BMP-10, BMP-11, BMP-12, BMP-15, BMP-3b, DPP; Vg1; Vgr; 60A protein; GDF-1;  
4 GDF-3, GDF-5, GDF-6, GDF-7, GDF-8, GDF-9, GDF-10, GDF-11; and morphogenically  
5 active amino acid sequence variants thereof.

1 52. The method of claim 29, 31, or 32 wherein said morphogenic protein is selected from the  
2 group consisting of: OP1; OP2, BMP2; BMP4; BMP5; BMP6; and morphogenically  
3 active amino acid sequence variants thereof.

1 53. The method of claim 29, 31, or 32 wherein said morphogenic protein is a morphogen, said  
2 morphogen comprising an amino acid sequence having at least 70% homology within the  
3 C-terminal 102-106 amino acids, including the conserved seven cysteine domain, of  
4 human OP1.

1 54. The method of claim 29, 31, or 32 wherein said morphogenic protein is OP1.

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- 1 55. The method of claim 29, 31, or 32 wherein said morphogenic protein is mature OP1  
2 solubilized in a saline solution.
- 1 56. The method of claim 29, 31, or 32 wherein said morphogenic protein comprises an amino  
2 acid sequence defined by OPX (Seq. ID No. 3); Generic Sequence 6 (Seq. ID No. 4,  
3 Generic Sequence 7 (Seq. ID No. 5); Generic Sequence 8 (Seq. ID No. 6); or Generic  
4 Sequence 9 (Seq. ID No. 7).
- 1 57. A composition for systemic administration of an morphogenic protein to a mammal, said  
2 composition comprising morphogenic protein in an amount sufficient to induce  
3 nonskeletal functional replacement tissue formation at a defect locus.
- 1 58. The composition of claim 57 wherein said composition comprises morphogenic protein  
2 dispersed in an aqueous solution.
- 1 59. The composition of claim 57 having a pH in the range of about 4-8.
- 1 60. The composition of claim 57 comprising physiologically buffered saline.
- 1 61. The composition of claim 57 wherein said morphogenic protein is provided at a  
2 concentration within the range of about 0.01 - 1000 mg/kg body weight.
- 1 62. The composition of claim 57 comprising a formulation for parenteral administration.
- 1 63. The composition of claim 57 formulated for oral administration.
- 1 64. The composition of claim 57 wherein said morphogenic protein is disposed in a  
2 biodegradable, biocompatible microsphere.
- 1 65. The composition of claim 57 comprising morphogenic protein in a concentration range of  
2 about 0.01 g/ml - 10.0 g/ml.
- 1 66. The composition of claim 57 comprising morphogenic protein in a con concentration  
2 range of about 0.1 g/ml - 1.0 g/ml.
- 1 67. The composition of claim 57 wherein said morphogenic protein is associated with a  
2 molecule competent to enhance solubility of said protein in aqueous media.

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- 1 68. The composition of claim 57 wherein said morphogenic protein comprises of the soluble  
2 complex form of said protein.
- 1 69. The composition of claim 57 further characterized as competent to enhance the rate of  
2 tissue formation at a local defect site.
- 1 70. The composition of claim 57 wherein said morphogenic protein is selected from the group  
2 consisting of: OP1; OP2, OP3, BMP2; BMP3; BMP4; BMP5; BMP6; BMP9; BMP-10,  
3 BMP-11, BMP-12, BMP-15, BMP-3b, DPP; Vg1; Vgr; 60A protein; GDF-1; GDF-3,  
4 GDF-5, GDF-6, GDF-7, GDF-8, GDF-9, GDF-10, GDF-11; and morphogenically active  
5 amino acid sequence variants thereof.
- 1 71. The composition of claim 57 wherein said morphogenic protein is selected from the group  
2 consisting of: OP1; OP2, BMP2; BMP4; BMP5; BMP6; and morphogenically active  
3 amino acid sequence variants thereof.
- 1 72. The composition of claim 57 wherein said morphogenic protein is a morphogen, said  
2 morphogen comprising an amino acid sequence having at least 70% homology within the  
3 C-terminal 102-106 amino acids, including the conserved seven cysteine domain, of  
4 human OP1.
- 1 73. The composition of claim 57 wherein said morphogenic protein is OP1.
- 1 74. The composition of claim 57 wherein said morphogenic protein is mature OP1 solubilized  
2 in a saline solution.
- 1 75. The composition of claim 57 wherein said morphogenic protein comprises an amino acid  
2 sequence defined by OPX (Seq. ID No. 3); Generic Seq. 6 (Seq. ID No. 4); Generic Seq.  
3 7 (Seq. ID No. 5); Generic Seq. 8 (Seq. ID No. 6); or Generic Seq. 9 (Seq. ID No. 7).
- 1 76. A method for inducing bone or cartilage formation at a defect locus in a mammal, the  
2 method comprising the step of administering osteogenic protein systemically to said  
3 mammal.
- 1 77. The method of claim 76 wherein said osteogenic protein is administered at a site distal to  
2 said locus.

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- 1 78. A method for enhancing the quantity or quality of callus formation at an osteogenic defect  
2 locus in a mammal, the method comprising the step of administering osteogenic protein  
3 systemically to said mammal at a site distal to said locus.
- 1 79. A method for enhancing the rate of bone or cartilage repair at a local defect site in a  
2 mammal, the method comprising the step of administering an osteogenic protein  
3 systemically to said mammal at a site distal to said locus.
- 1 80. The method of claim 76, 78 or 79 wherein said defect locus defines a bone fracture.
- 1 81. The method of claim 76, 78, or 79 wherein said defect locus defines a volume incapable of  
2 endogenous repair.
- 1 82. The method of claim 76, 78, or 79 wherein said defect locus defines an osteochondral  
2 defect.
- 1 83. The method of claim 76, 78, or 79 wherein said mammal is a human.
- 1 84. The method of claim 83 wherein said human has a reduced capacity to induce callus  
2 formation.
- 1 85. The method of claim 83 wherein said human is afflicted with impaired blood flow to the  
2 skeletal extremities.
- 1 86. The method of claim 83 wherein said individual has a reduced capacity to induce an  
2 endogenous osteoinductive signal.
- 1 87. The method of claim 76, 78, or 79 wherein osteogenic protein is administered  
2 parenterally.
- 1 88. The method of claim 87 wherein osteogenic protein is administered intravenously.
- 1 89. The method of claim 76, 78, or 79 wherein said osteogenic protein is administered orally.
- 1 90. The method of claim 76 wherein said osteogenic protein is administered to said individual  
2 at a time when mesenchymal progenitor cells are accessible to said defect locus.



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- 1 91. The method of claim 76, 78, or 79 wherein said osteogenic protein is administered at least  
2 six hours after the creation of said defect.
- 1 92. The method of claim 76 or 79 wherein said osteogenic protein is administered at least 24  
2 hours after the creation of said defect.
- 1 93. The method of claim 76 or 79 wherein said osteogenic protein is administered at least 72  
2 hours after the creation of said defect.
- 1 94. The method of claim 76, 78, or 79 wherein said osteogenic protein is administered to said  
2 mammal after the initiation of fibrosis at said defect locus.
- 1 95. The method of claim 76, 78, or 79 wherein said osteogenic protein is administered in  
2 aqueous solution.
- 1 96. The method of claim 83 wherein said human is a steroidal drug user.
- 1 97. The method of claim 83 wherein said human is aged, obese, or afflicted with osteopenia or  
2 diabetes.
- 1 98. The method of claim 76, 78, or 79 wherein said osteogenic protein is selected from the  
2 group consisting of: OP1; OP2, OP3, BMP2; BMP3; BMP4; BMP5; BMP6; BMP9;  
3 BMP-10, BMP-11, BMP-12, BMP-15, BMP-3b, DPP; Vgl; Vgr; 60A protein; GDF-1;  
4 GDF-3, GDF-5, GDF-6, GDF-7, GDF-8, GDF-9, GDF-10, GDF-11; and morphogenically  
5 active amino acid sequence variants thereof.
- 1 99. The method of claim 76, 78, or 79 wherein said osteogenic protein is selected from the  
2 group consisting of: OP1; OP2, BMP2; BMP4; BMP5; BMP6; and morphogenically  
3 active amino acid sequence variants thereof.
- 1 100. The method of claim 76, 78, or 79 wherein said osteogenic protein is a morphogen, said  
2 morphogen comprising an amino acid sequence having at least 70% homology within the  
3 C-terminal 102-106 amino acids, including the conserved seven cysteine domain, of  
4 human OP1.
- 1 101. The method of claim 76, 78, or 79 wherein said osteogenic protein is OP1.

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- 1 102. The method of claim 76, 78, or 79 wherein said osteogenic protein is mature OP1  
2 solubilized in a saline solution.
- 1 103. The method of claim 76, 78, or 79 wherein said osteogenic protein comprises an amino  
2 acid sequence defined by OPX (Seq. ID No. 3); Generic Sequence 6 (Seq. ID No. 4,  
3 Generic Sequence 7 (Seq. ID No. 5); Generic Sequence 8 (Seq. ID No. 6); or Generic  
4 Sequence 9 (Seq. ID No. 7).
- 1 104. A composition for systemic administration of an osteogenic protein to a mammal, said  
2 composition comprising osteogenic protein in an amount sufficient to induce bone or  
3 cartilage formation at a skeletal defect locus.
- 1 105. The composition of claim 104 wherein said composition comprises osteogenic protein  
2 dispersed in an aqueous solution.
- 1 106. The composition of claim 104 having a pH in the range of about 4-8.
- 1 107. The composition of claim 104 comprising physiologically buffered saline.
- 1 108. The composition of claim 104 wherein said osteogenic protein is provided at a  
2 concentration within the range of about 0.01 - 1000 mg/kg body weight.
- 1 109. The composition of claim 104 comprising a formulation for parenteral administration.
- 1 110. The composition of claim 104 formulated for oral administration.
- 1 111. The composition of claim 104 wherein said osteogenic protein is disposed in a  
2 biodegradable, biocompatible microsphere.
- 1 112. The composition of claim 104 comprising osteogenic protein in a concentration range of  
2 about 0.01 g/ml - 10.0 g/ml.
- 1 113. The composition of claim 104 comprising osteogenic protein in a concentration range  
2 of about 0.1 g/ml - 1.0 g/ml.
- 1 114. The composition of claim 104 wherein said osteogenic protein is associated with a  
2 molecule competent to enhance solubility of said protein in aqueous media.

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- 1 115. The composition of claim 104 wherein said osteogenic protein comprises of the soluble  
2 complex form of said protein.
- 1 116. The composition of claim 104 further characterized as competent to enhance the rate of  
2 bone formation at a local fracture site.
- 1 117. The composition of claim 104 wherein said osteogenic protein is selected from the group  
2 consisting of: OP1; OP2, OP3, BMP2; BMP3; BMP4; BMP5; BMP6; BMP9; BMP-10,  
3 BMP-11, BMP-12, BMP-15, BMP-3b, DPP; Vg1; Vgr; 60A protein; GDF-1; GDF-3,  
4 GDF-5, GDF-6, GDF-7, GDF-8, GDF-9, GDF-10, GDF-11; and morphogenically active  
5 amino acid sequence variants thereof.
- 1 118. The composition of claim 104 wherein said osteogenic protein is selected from the group  
2 consisting of: OP1; OP2, BMP2; BMP4; BMP5; BMP6; and morphogenically active  
3 amino acid sequence variants thereof.
- 1 119. The composition of claim 104 wherein said osteogenic protein is a morphogen, said  
2 morphogen comprising an amino acid sequence having at least 70% homology within the  
3 C-terminal 102-106 amino acids, including the conserved seven cysteine domain, of  
4 human OP1.
- 1 120. The composition of claim 104 wherein said osteogenic protein is OP1.
- 1 121. The composition of claim 104 wherein said osteogenic protein is mature OP1 solubilized  
2 in a saline solution.
- 1 122. The composition of claim 104 wherein said osteogenic protein comprises an amino acid  
2 sequence defined by OPX (Seq. ID No. 3); Generic Seq. 6 (Seq. ID No. 4); Generic Seq.  
3 7 (Seq. ID No. 5); Generic Seq. 8 (Seq. ID No. 6); or Generic Seq. 9 (Seq. ID No. 7).